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Epidemiological and animal studies associate high levels of dietary fat with increased risk of sex hormone mediated cancer, such as breast cancer. A high intake of total fat and omega-6 fatty acids increases risk while omega-3 (n3) fatty acids are associated with risk reduction. Our proposal is testing the effect of dietary fat and fatty acids on sex hormone concentrations in post-menopausal women. The objectives are to evaluate 1) the effects of total fat and n3 intake on plasma and urinary sex hormone levels, 2) the relationship between plasma fatty acids and plasma and urinary sex hormones, and 3) the effects of total fat and n3 on the association between sex hormone concentrations and urinary prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). We are performing a randomized, Latin square-designed controlled feeding study testing High Fat, Low Fat, and Low Fat + n3 diets, each of 8 week duration. In order to determine the estrogenic effects of the diets, sex hormone endpoints will be measured reflecting availability, metabolism, and action. Plasma fatty acids fractions and urinary PGE<sub>2</sub> will be measured to evaluate mechanistic effects. At present 88 women have been screened by telephone, 23 have been screened in the clinic, 17 have been enrolled in the trial. Eleven subjects have completed all aspects of the trial. Initial data analysis is being started this summer of the sex hormone samples. No data has yet been generated.

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## **Introduction**

Our project addresses important questions about the effects of dietary total fat and fatty acids on sex hormone concentrations in postmenopausal women. The study is being conducted at the General Clinical Research Center of the University of Minnesota. Our guiding hypothesis is that dietary total fat and fatty acid content affect sex hormone concentrations in a manner associated with sex hormone mediated cancer risk. The specific objectives are 1) to evaluate the effects of total fat and omega-3 fatty acid intake on plasma and urinary sex hormone levels in postmenopausal women, 2) to evaluate the relationship between plasma concentrations of specific fatty acids and concentrations of plasma and urinary sex hormones, and 3) to evaluate the effects of total fat and omega-3 fatty acids on the association between sex hormone concentrations and urinary prostaglandin E<sub>2</sub> and thromboxane B<sub>2</sub> concentrations.

We are conducting a well controlled feeding study to evaluate the role of fat and fatty acids in 24 healthy, postmenopausal women. The diets being tested include a "high risk" American diet (40% fat), a low fat diet (20% fat) and a low fat diet with supplemental omega-3 fatty acids (23% fat). Endpoints are being measured to assess availability, metabolism, and action of sex hormones in response to the diets. Plasma fatty acids fractions and urinary prostaglandin E<sub>2</sub> is being measured to evaluate mechanistic effects of dietary fat.

Increased understanding of the mechanisms by which dietary fat affect sex hormone action may provide critical information for the development of cancer-preventative dietary recommendations. Nutrition information provided as focused guidelines regarding fat intake can be developed for public use that indicate which types of foods to include in the daily diet and which to avoid.

## **Body**

### ***Study Progress:***

The project is proceeding along the time line as defined in our statement of work. We received final approval to initiate the project from the University of Minnesota Human Subject Protection Program/Internal Review Board on 10/29/2004. A no-cost extension has been granted for 1 year.

Extensive recruitment efforts are ongoing. We advertise throughout the medical campus and surrounding campus buildings and through a text ad in the Fairview University Medical Center staff and patient flier. To date 88 subjects have been screened by telephone, 23 subjects have been screened at the research center and 17 subjects have been enrolled in the feeding trial. Of these subjects, 11 have completed all aspects of the study.

### ***Personnel:***

The following personnel are presently supported on this grant  
Susan Raatz PhD RD, Principle Investigator (5% effort)  
Mindy Kurzer PhD, Co-investigator (5% effort)  
J Bruce Redmon MD, Co-investigator (5% effort)  
Michael Walcher, Senior Scientist (25% effort)

Julie Huyck, Student Food Service Worker (75% effort)  
Lindsay Orr BA, Graduate Research Assistant – Currently funded on a DOD Predoctoral Fellowship based on this project

### **Key Research Accomplishments**

Sex hormone data analysis for 5 subjects has been completed. These preliminary data showed that within subjects, 8 weeks consumption of a LF $\omega$ 3 significantly decreased plasma E<sub>2</sub> concentrations in postmenopausal women. Compared to HF, consumption of the LF $\omega$ 3 significantly decreased E<sub>2</sub> concentrations between groups at 8 weeks.

Eicosanoid, fatty acid, and remaining sex hormone samples will begin to be analyzed the summer.

### **Reportable Outcomes**

#### ***Training:***

Lindsay Orr, BA, a graduate student in Human Nutrition, received a DOD Breast Cancer Research Program predoctoral traineeship award (Award #W81XWH-06-1-0778) in August of 2006 based on this study. This grant will fund Ms. Orr to work on this project as part of her predoctoral training and includes yearly travel from Sept 2006 through October 2009.

Support from this project assisted Lindsay Orr in the attendance of the Nutrition and Cancer Prevention Practicum March 20-24, 2006 at the National Cancer Institute in Rockville, MD. NIH

#### ***Data Presentation:***

"Dietary Fat, Eicosanoids and Breast Cancer Risk" was presented as a poster session on September 11, 2006 at the University of Minnesota Women's Health Research Conference (see Appendix 1).

### **Conclusions**

The study is progressing as projected on the "Statement of Work". Given the nature of a long term feeding trial, no reportable data has yet been obtained. The study progress is as expected with recruitment of participants proceeding smoothly. The test diets are well accepted by the participants, all endpoint visits have gone well.

### **References**

None

## **Appendix 1: Women's Health Seminar Poster Presentation (abstract)**

Effect of Dietary Fat and Fatty Acids On Plasma Sex Hormone Profiles in Postmenopausal Women.

Lindsay Orr, Steve McColley, J Bruce Redmon MD, Mindy Kurzer PhD, Susan Raatz PhD RD. Departments of Medicine and Food Science and Nutrition, University of Minnesota, Minneapolis, MN

Background: Sex hormone mediated cancers, such as breast, present a significant problem in the United States. It is important to develop safe and effective preventative strategies for these diseases. Epidemiological evidence and animal studies show that dietary fat is associated with risk of development of sex hormone mediated cancer. Specifically that a high intake of omega-6 fatty acids increases risk while omega-3 fatty acids are associated with risk reduction. Although the associations between dietary fat and sex hormone mediated cancers is unclear, it is likely due to mechanisms of endocrine balance, eicosanoid production, or immune function.

Objective/Hypothesis: The primary objective of this investigation is to determine whether diets designed to increase plasma omega-3 fatty acid concentrations (a low fat diet, with or without omega-3 fatty acid enrichment), will favorably affect sex hormone distribution in postmenopausal women in a direction associated with reduced risk of sex hormone-mediated cancer development. The specific aims of this study are to evaluate the effects of total fat and omega-3 fatty acid intake on plasma sex hormone levels in postmenopausal women.

Study Design: In order to evaluate these relationships we are conducting a well-controlled feeding study to evaluate dietary fat and fatty acid effects. The diets being tested in 8 week feeding periods include a "high risk" American diet (40% fat; HF), a low fat diet (20% fat; LF) and a low fat diet with supplemental omega-3 fatty acids (23% fat; LF $\omega$ 3). Endpoint measures of plasma sex hormones were obtained at baseline, 4, and 8 weeks of each dietary treatment.

Results: Plasma estradiol ( $E_2$ ), estrone ( $E_1$ ), estrone sulfate ( $E_1$ -S), testosterone, androstenedione (AS), sex hormone binding globulin (SHBG), follicle stimulating hormone, dehydroepi-androsterone (DHEA), and dehydroepiandrosterone sulfate were analyzed by radio-immunoassay for five participants. A trend for increased concentrations from baseline to 8 weeks was detected for plasma AS, DHEA, and  $E_2$  with HF, and for  $E_1$ -S with LF. A trend for decreased concentration of plasma SHBG was observed after 8 weeks of LF. Consumption of the LF $\omega$ 3 decreased  $E_2$  concentrations significantly from baseline to 8 weeks ( $10.6 \pm 1.0$  nmol/L to  $7.3 \pm 0.6$  nmol/mL;  $p = 0.012$ ). A trend for increased DHEA levels was observed after consumption of the LF $\omega$ 3 at 8 weeks compared to LF.  $E_2$  concentrations were significantly higher following consumption of the LF vs. LF $\omega$ 3 at 8 weeks ( $10.3 \pm 0.8$  nmol/L vs.  $7.3 \pm 0.6$  nmol/L;  $p = 0.032$ ).

Conclusions: Preliminary data showed that within subjects, 8 weeks consumption of a LF $\omega$ 3 significantly decreased plasma E<sub>2</sub> concentrations in postmenopausal women. Compared to HF, consumption of the LF $\omega$ 3 significantly decreased E<sub>2</sub> concentrations between groups at 8 weeks. These data are preliminary results - the effects of the three diets on plasma sex hormone profile will be further elucidated as more subjects complete the study.